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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,951	08/28/2003	Jia-He Li	70003.0002USD1	6259

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CONNOLLY BOVE LODGE & HUTZ LLP
SUITE 800
1990 M STREET NW
WASHINGTON, DC 20036-3425

EXAMINER	
COVINGTON, RAYMOND K	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/649,951	VAN DER LINDEN ET AL.	
	Examiner	Art Unit	
	Raymond Covington	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Upon reconsideration the rejections under 35 USC 112 and 35 USC 103 have been withdrawn in light of applicants' amendment and comments of 6/9/05. The amendments resolve the 112 issues. The prior art neither teaches nor suggests the compounds as presently recited in the claims. There is no suggestion or motivation for aromatic ring containing Z groups on the formula IV compound.

Pursuant to current Restriction practice, claims 58-60 have been reconsidered for rejoinder and will be searched too the extent they read on the elected subject matter.

NEW REJECTION

indication of allowable subject matter is withdrawn in view of the following rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 47-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. Specifically, the claims contain the phrase "prodrug" which is not adequately described in the specificatio. The specification only provides description for a pharmaceutical composition comprising the compound of formula IV and a pharmaceutical acceptable carrier.

Claims 47-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

The specification does not give any guidance as to how each of the heterocyclic substituted Z derivatives were prepared. In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described. They are:

1. the nature of the invention,

2. the state of the prior art,

3. the predictability or lack thereof in the art,

4. the amount of direction or guidance present,

5. the presence or absence of working examples,

6. the breadth of the claims,

7. the quantity of experimentation needed, and

8. the level of the skill in the art.

In the instant case, Applicants are claiming disubstituted flouranthene derivatives. Applicants have not disclosed any working examples, which would demonstrate, or guide, one skilled in the art as to how the aryl or heterocyclic disubstituted flouranthene derivatives other than pyridine and pyrrole were prepared or obtained. See, for example, table 1 and examples 36, 53, 54 and 55.

There is insufficient disclosure of starting materials that would place such a diverse genus of compounds in possession of the public in the event of a patent grant. In addition, there is no reasonable assurance that such an alleged genus of compounds would possess all of the alleged properties for use. See In re Fouche 169 USPQ 429 ((CCPA 1971)). Quite clearly, more than routine experimentation would be required to place the claimed compounds, compositions and methods of use in possession of the public in the event of a patent grant.

The specification must teach how to make the invention. *In re Gardner*, 166 U.S.P.Q. 138 (1970). In order to practice the claimed invention, one skilled in the art would have speculate how the derivatives were obtained or prepared. Therefore,

the instant invention is not enabled. Claims limiting the scope of these terms should overcome this rejection.

Claims 58-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors include 1) the breadth of the claims, 2) the nature of the invention, 3) the state of the prior art, 4) the level of one of ordinary skill, 5) the level of predictability in the art, 6) the amount of direction provided by the inventor, 7) the existence of working examples, and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention: The nature of the invention is drawn to a method of modulating or inhibiting PARG using a compound of claim 47.

The state of the prior art and predictability: The state of the prior art is that it involves screening in vitro and in vivo to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instantly claimed invention is highly unpredictable given the unpredictability of treating all diseases and disorders selected from acute pain,
Arthritis, atherosclerosis, cachexia, cardiovascular disorders, chronic pain, degenerative diseases, diabetes, head trauma hyperglycemia immune senescence inflammatory bowel disorders, ischemia macular degeneration muscular dystrophy, tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases, neuronal tissue damage or disease, neuropathic pain nervous insult. osteoarthritis osteoporosis, peripheral nerve

injury, renal failure, resuscitated hemorrhagic shock, retinal ischemia septic shock skin aging, vascular stroke, diseases or disorders relating to lifespan or proliferative capacity of cells, and diseases or disease conditions induced or exacerbated by cellular senescence.

Guidance and working examples: Compounds according to the invention have been made. The assay test is noted. While screening test in an assay provides data in picking and choosing lead compounds for further testing, screening test per se does not provide sufficient operational guidance in an 'individual' in patho-physiological environment.

It is not clear that the assays correlate to any form of PARG treatment. There is no evidence of functional treatment, i.e. no correlation to treatment in humans. It has yet to be established that the claimed compounds have a viable utility which is why they are included in the rejection.

The 'how to use' requirements of 35 USC 112 are not met by disclosing only a pharmaceutical activity of the clamed compounds if one skilled in the art would not be able to use the compounds effectively without undue experimentation. More than mere assertions or screening data is needed unless one of ordinary skill in the art would accept the utility statement as obviously valid and correct. The instantly claimed compounds are not structurally similar to known compounds

having the same activity and their pharmacological properties can not be predicted from their chemical structure, thus a disclosure that they possess a particular activity is not enough. See Tan et al Hepatitis C Therapeutics: CURRENT STATUS AND EMERGING STRATEGIES, Nature Reviews, Drug Discover, Vol. 1, November 2002, 867-881, page 871, Table 1, teach several drugs (not structurally similar to the claimed compounds) that are used to treat HCV.

Further, many of the diseases or disorders named are in fact a CLASS of disorders or diseases. No single compound or class of compounds is known to treat all the sub-categories of a particular type of disease or disorder. By way of example, applicants name diseases or disorders associated with all disorders that in some way relate to life span, all types of pain, all types of aging, any kind of head trauma. Applicants' are attempting to claim every known associated disease or disorder with the above conditions as well as future diseases and disorders and such is wholly inoperable.

The instant specification does not adequately describe or enable the nexus between the modulation of PARG and a useful treatment of a disease/condition. Modulation of PARG involves antagonism, inhibition, agonism and others. These modulations are sometimes opposite reactions. It is not seen where the instant specification adequately describes the nexus

between the modulation of PARG and a useful treatment of a single disease or condition.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the compound of claim 47 and PARG, one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 47 due to the unpredictability of the role of PARG, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

Claims 55-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not teach how to use the compounds. In this field of highly unpredictable, extremely difficult art, the specification provided no specific compound with data of dosage or efficacy information, and thus lacked description and enablement of how the claimed scope can be operated.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond Covington whose telephone number is (571) 272-0681. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, C. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond Covington
Examiner
Art Unit 1625

RKC

10/17/05